Summary Basis for Regulatory Action

Date	06 June 2014
From	Nancy Kirschbaum, PhD, Committee Chair
Subject	Summary Basis for Regulatory Action
BLA No.	STN BL 125487/0
Applicant	Biogen Idec, Inc.
Date of Submission	07 March 2013
PDUFA Goal Date	07 June 2014
Trade Name/Proper Name	ELOCTATE™/Antihemophilic Factor (Recombinant), Fc Fusion Protein
Dosage form	Lyophilized powder with nominal potencies: 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU or 3000 IU per vial
Proposed Indication(s)	Indicated in adults and children with Hemophilia A for: • Control and prevention of bleeding episodes, • Perioperative management, • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. ELOCTATE™ is not indicated for the treatment of von Willebrand Disease.
Recommended Action	Approval
Signatory Authority Action	Jay Epstein, MD_____ *Offices Signatory Authority* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum* Mary Anne Malarkey_____ *Offices Signatory Authority* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum*

Discipline Review	
Clinical Review	Lisa Faulcon
Clinical Pharmacology Review	Carl-Michael Staschen
Statistical Review	Judy Li
Chemistry, Manufacturing and Controls Review	Jie He, Ellen Huang, Nancy Kirschbaum, Andrey Sarafanov, Ze Peng
Pharmacology / Toxicology Review	M. Keith Wyatt, Anne M. Pilaro
Bioresearch Monitoring Review	Christine Drabick
Pharmacovigilance Review	Wambui Chege
Human Factors Evaluation Review	QuynhNhu Nguyen
Labeling Review	Loan Nguyen, Nisha Jain, Lisa Faulcon, Nancy Kirschbaum, Carl-Michael Staschen, Wambui Chege
Lot Release Coordination /In-Support Testing	Karen Campbell, Lokesh Bhattacharyya, Igor Bacik, Hyesuk Kong, James Kenney, Tao Pan, Mark Levi, Alfred Del Grosso
Regulatory Project Manager	Leigh Pracht, Nannette Cagungun

1. Introduction

Biogen Idec, Inc. (Biogen) has submitted an original biologics license application (BLA) to seek US licensure for Antihemophilic Factor (Recombinant), Fc Fusion Protein. The commercial product is a lyophilized powder in a crimp-sealed, stoppered, glass vial, available in nominal potencies of 250, 500, 750, 1000, 1500, 2000 or 3000 international units (IU). The product is reconstituted with sterile water for injection provided in a pre-filled syringe. The proprietary name of the US marketed product is ELOCTATE™.

ELOCTATE™ is indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: (1) control and prevention of bleeding episodes, (2) perioperative management, and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes. ELOCTATE™ is not indicated for the treatment of von Willebrand Disease.

2. Background

Hemophilia A is a rare, hereditary, hematologic disorder caused by deficiency or dysfunction of Coagulation Factor VIII (historically referred to as Antihemophilic Factor), resulting in bleeding secondary to abnormal clot formation. Because the Factor VIII gene is located on the X-chromosome, Hemophilia A has an X-linked, recessive inheritance pattern, affecting 1 in 5,000 male births with rare occurrence in females. There is no available cure for Hemophilia A. To promote clotting, patients are treated to replace the deficient Factor VIII by intravenous administration of a purified Coagulation Factor VIII (Antihemophilic Factor) concentrate. Both plasma derived and recombinant DNA derived Antihemophilic Factor concentrates are commercially available. In recent years, treatment regimens have shifted from on-demand treatment of bleeding episodes to routine prophylaxis because of observed improvement in long-term clinical outcome. Routine prophylaxis regimens have been hampered, however, by the short circulating half-life of infused Factor VIII (mean 12 hr.) leading to frequent product infusions. ELOCTATE™, Antihemophilic Factor (Recombinant), Fc Fusion Protein [rAHFFc], was designed to provide a longer acting, coagulation active, Antihemophilic Factor concentrate for less frequent dosing in routine prophylaxis regimens for Hemophilia A patients.

B-domain deleted, recombinant Factor VIII, Fc Fusion Protein (BDD-rFVIIIFc), is the active ingredient in ELOCTATE™. The Factor VIII portion of the molecule is a recombinant analogue of human Coagulation Factor VIII that contains a full length, N-terminal heavy chain and a full length, C-terminal light chain, but deletes 894 of 908 amino acids from the B-domain located in the middle. The Fc portion is a recombinant analogue of the human IgG_1, -b(4)----bonded Fc domain containing the hinge, CH2 and CH3 regions. BDD-rFVIIIFc comprises 1890 amino acids, post-translational modifications comparable to endogenous Factor VIII and has an apparent molecular weight of approximately 220 kDa. The majority of the expressed protein is proteolytically processed to a two chain molecule; however, ELOCTATE™ may also contain up to 39% of a single chain, non-processed form. Both molecules have been shown to have comparable Factor VIII activity.

Clinical trials that provided the evidence for safety and efficacy of ELOCTATE™ were conducted under IND 14134. To support licensure for the proposed indications, the clinical development program included: (1) a pharmacokinetic (PK) study and (2) an open-label,

partially randomized trial where subjects received either one of two prophylaxis regimens (individualized or fixed weekly) or on-demand treatment for acute bleeding episodes for at least 50 exposure days (ED). In addition, a subset of subjects enrolled in the partially randomized trial received ELOCTATE™ for perioperative management. Interim analysis data from an ongoing PK and safety study in pediatric subjects were also considered. Biogen has agreed to complete three post-marketing commitment studies: (1) an ongoing extension study evaluating the long-term efficacy and safety of ELOCTATE™, (2) an ongoing pediatric study evaluating the safety and efficacy of ELOCTATE™ in previously treated patients <12 years of age, and (3) a safety and efficacy trial in previously untreated patients.

ELOCTATE™ is not currently approved or marketed in any country.

This original BLA was reviewed under the PDUFA V program (standard 12 month) and included the review milestones listed in Table 1.

Table 1: Review Milestones

Milestone	Date
Received	07 March 2014
Filed	07 May 2014
Mid-cycle Communication	10 September 2013
Major amendment	04 December 2013
Late Cycle Meeting	03 April 2014
Action Due	07 June 2014

3. Chemistry, Manufacturing and Controls (CMC)

Chemistry, Manufacturing and Controls significant issues resolved during BLA review

- *Process validation*: Initial process validation was deficient in that designated conformance lots for 500 IU, 750 IU, 1000 IU, 1500 IU and 2000 IU nominal potencies were analyzed under a retrospective protocol. The retrospective validation was considered inadequate because it presented an inherently biased approach in which clinical lots manufactured before initiation of process validation were retrospectively analyzed. At mid-cycle, Biogen was asked to manufacture the following conformance lots under a prospective protocol: (a) 500 IU potency, small lot size, (b) 1000 IU potency, small lot size and (c) 2000 IU potency, large lot size. Amendment 27 contained prospective validation protocols. Amendment 37 contained process validation study reports, which were considered adequate to fulfill requirements for process validation.
- *Validation of the lyophilization process:* Biogen initially provided the results of lyophilization technical runs, lyophilization parameter operating range studies, and retrospective process consistency validation runs to demonstrate validation of the lyophilization process. The studies provided insufficient data to support the final lyophilization cycle. Deficiencies included: failure to conduct prospective process consistency validation runs, failure to provide an adequate empty chamber shelf temperature mapping study, failure to perform a full-scale product temperature mapping study, and failure to perform any extended sampling of either the maximum or minimum lyophilization loads. Biogen provided the lyophilizer qualification protocol for the empty chamber study and technical runs with –b(4)---------- in amendment 23. Prospective process validation protocols were submitted in amendment 27, which was considered by CBER as a major

amendment. Biogen provided reports on empty chamber shelf temperature mapping studies, product temperature mapping studies and extended sampling results of the maximum and minimum lyophilization loads for the –b(4)---------- product potencies, in amendment 36. Process validation study reports were submitted in amendment 37. FDA found the information contained in these amendments to be acceptable.

- *Establishment of in-process controls that reflect manufacturing capability*: Biogen's originally proposed in-process specifications (IPS) for –b(4)---------- far exceeded values obtained during manufacture with the validated process. They were, therefore, considered inadequate for proper routine, commercial process control. At mid-cycle, the Agency requested that Biogen establish IPS more reflective of manufacturing experience. Biogen proposed revised acceptance limits in amendment 30; however, the proposed limits still far exceeded manufacturing experience and were not acceptable to the Agency. Biogen further revised IPS for –b(4)---------- in amendment 40, which were considered acceptable by the Agency.
- *Complete information about the manufacture, control and safety of critical reagent, --b(4)*---------- ---: At mid-cycle, Biogen was informed that the Regulatory Support File provided by –b(4)--------- and submitted to the BLA was not adequate to ensure continued quality of the purchased –b(4)----. Since b(4)---------- did not want to submit a master file, Biogen agreed to provide detail regarding -b(4)- manufacture and control consistent with FDA guidance for –b(4)---------- used as reagents, and committed to enhanced material controls. In amendment 30, Biogen committed to implementing enhanced receipt testing for each –b(4)---lot and notification to CBER following any changes to –b(4)- manufacture or control. Detailed quality information was submitted in amendment 35 and considered adequate.
- *Potency Labeling of Drug Product Vials*: Factor VIII potency can be determined using either of two analytical methodologies: (1) one stage clotting assay [OS] or (2) chromogenic substrate assay [CS]. In Europe, the CS assay is mandated due to better precision. In the US, the OS assay is preferred because it is the assay used in clinical laboratories. For highly purified, recombinant products, discrepancies between the two methodologies have been reported. Therefore, Biogen Idec designed pre-market development programs to use both assays for comparative analysis of product potency and patient recovery. Having considered these data, Biogen proposed to label its commercial product using the CS assay. Biogen justified acceptability of the CS assay through: (a) demonstration of a systematic correlation between OS and CS potencies for drug product vials, (b) comparable pharmacokinetic outcome parameters and (c) field study results that indicated ability for effective clinical management in US clinical laboratories employing OS assays. Therefore, FDA accepted Biogen's proposal to use the CS assay for potency labeling.

a) Product Quality and Manufacturing Control

Description

ELOCTATE™, Antihemophilic Factor (Recombinant), Fc Fusion Protein [rAHFFc] is a sterile, non-pyrogenic, lyophilized powder for reconstitution for intravenous injection. The product is supplied in single use vials containing nominal potencies of 250, 500, 750, 1000, 1500, 2000 or 3000 international units (IU). Each vial of ELOCTATE™ is labeled with the actual content in IU. The powder for injection is reconstituted with 3 mL sterile water for injection (SWFI) supplied in a sterile pre-filled syringe. The reconstituted product contains the excipients: sucrose,

sodium chloride, L-histidine, calcium chloride and polysorbate 20. ELOCTATE™ contains no preservatives.

The active ingredient in ELOCTATE™ is a B-domain deleted, recombinant Factor VIII (BDD-rFVIII) construct covalently linked to the dimeric Fc domain of IgG_1 without intervening sequences. Both BDD-rFVIII and rFc domains are derived from respective human sequences. Figure 1 illustrates the structure of BDD-rFVIIIFc.

[b(4)]

Analytical Characterization

Several lots of clinical and commercial scale –b(4)---------- drug product were characterized for primary sequence, post-translational modifications including –b(4)---------- purity, potency and microbial safety. –b(4)----------. A robust program of analytical comparability supported pre-market manufacturing and clinical development.

Representative reference standards were established, which were extensively characterized for --b(4)---------. Biogen has qualified a primary reference standard and established a robust reference standard program designed to link commercial product to clinical material and mitigate against quality attribute drift over time.

Impurities

Product and process related impurities were identified and characterized in several batches of drug substance and drug product that were studied in clinical trials. Removal of product and process related impurities by the commercial manufacturing process was demonstrated during process development and process validation.

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BDD-rFVIIIFc is produced from a human embryonic kidney (HEK) cell line. –b(4)--- ----------
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Drug Product Release Specification

The drug product release specification was derived from analysis of several development lots, many of which were studied in clinical trials. The final product release specification in Table 2 is considered adequate to confirm product quality and manufacturing consistency.

Table 2: Final Product Release Specification

Attribute/Test	Method	Acceptance Criteria
General characteristics		
Appearance	Visual inspection	White to off-white cake to powder
Residual Moisture	--b(4)---------- ---	--b(4)----------
Appearance after reconstitution	Visual inspection	--b(4)---------- ---------- ----------
Reconstitution time	--b(4)----------	--b(4)----------
--b(4)----------	--b(4)----------	--b(4)----------
--b(4)----------	--b(4)----------	--b(4)----------
Identity		
--b(4)----------	--b(4)---------- ----------	--b(4)----------
--b(4)----------	--b(4)----------	--b(4)----------
Potency		
Factor VIII potency	Chromogenic substrate assay	250 IU vial: --b(4)---------- 500 IU vial: --b(4)---------- 750 IU vial: --b(4)---------- 1000 IU vial: --b(4)---------- 1500 IU vial: --b(4)---------- 2000 IU vial: --b(4)---------- 3000 IU vial: --b(4)---------- --b(4)----------
--b(4)----------	--b(4)----------	--b(4)----------
Purity and Impurities		
Purity	--b(4)----------	--b(4)---------- ---------- ----------
--b(4)----------	--b(4)---------- ----------	--b(4)----------
Excipients		
Calcium chloride	--b(4)----------	--b(4)----------
L-histidine	--b(4)----------	--b(4)----------
NaCl	--b(4)---------- ----------	--b(4)----------
Sucrose	--b(4)----------	--b(4)----------
Polysorbate 20	--b(4)----------	--b(4)----------
Quantity		
--b(4)----------	--b(4)---------- ----------	--b(4)----------
Safety		
Particulates	--b(4)----------	--b(4)----------

Attribute/Test	Method	Acceptance Criteria
Endotoxin	--b(4)----------	--b(4)---------- ---------- ----------
Sterility	--b(4)----------	No growth

Manufacturing Control

Process Description

BDD-rFVIIIFc drug substance is produced from –b(4)---------- ----------
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Source Material Quality and Control

Human Embryonic Kidney (HEK) cell substrate, HEK293H was the parent cell line used to generate ----b(4)-- ----------
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---------- were characterized for adventitious agents safety, genotypic quality and phenotypic quality consistent with recommendations in ICH and FDA guidance. –b(4)----- -------
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Thereafter, the –b(4)----------. The manufacturing process for ELOCTATE™ does not use materials or reagents of animal or human origin.

Critical Process Steps

The manufacturing process for BDD-rFVIIIFc drug substance incorporates –b(4)- manufacturing steps validated to clear relevant viruses: (1) a detergent inactivation step, (2) a nanofiltration step -------b(4)----------

Critical Process Parameters and Their Control

Biogen implemented quality risk assessment tools and process characterization studies to define an in-process control strategy and terminology consistent with definitions in the Q8(R2) guideline and accepted industry practice. Process inputs (operational controls) and process outputs (quality controls) have been categorized as critical, key or non-key parameters according to determined potential product or process performance impact. Non-key process inputs (N-KCP) are controlled by monitoring operating ranges. Critical (CCP) or key (KCP) inputs are

controlled by action limits. Critical outputs [termed, "critical in-process controls (CIPC)" or "critical in-process tests (CIPT)"] are controlled through action limits or in-process specifications (IPS). In-process controls for each manufacturing operation have been established and justified.

Process Validation

Biogen successfully manufactured –b(4)- consecutive drug substance conformance batches at the Cambridge, MA facility, the intended commercial site, under a prospective process validation protocol.

Three, 250 IU and three, 3000 IU drug product conformance lots were successfully manufactured at the intended commercial contract facility, under a prospective process validation protocol. During BLA review, FDA asked Biogen to validate the process for intermediate product potencies: 500 IU, 750 IU, 1000 IU, 1500 IU and 2000 IU through manufacture under a prospective protocol of the following conformance lots: (a) 500 IU potency, small lot size, (b) 1000 IU potency, small lot size and (c) 2000 IU potency, large lot size. Biogen submitted process validation reports from successful conformance lot manufacture in amendment 37.

Process and quality controls for drug substance conformance batch and drug product conformance lot manufacture complied with prospectively defined acceptance criteria to fulfill requirements for successful process validation.

Analytical Methods

Suitable analytical methods have been validated to support quality control throughout manufacture, final product release and stability monitoring. An acceptable reference standard qualification and maintenance program has been established.

Container/Closure System

BDD-rFVIIIFc drug substance is stored at –b(4)----------. The primary container closure system for all drug product presentations consists of a –b(4)-------- glass vial closed with a –b(4)---------- stopper and sealed with a 20 mm aluminum flip-off crimp seal. Seal colors are different for each nominal potency. The reconstitution diluent is contained in a ---b(4)---- sterilized, prefilled –b(4)-- glass syringe barrel sealed with a –b(4)---------- plunger and tamper proof tip cap. Dimensional drawings, specifications and letters of authorization to applicable master files for each component were provided. Container closure safety and performance were qualified through extractables, leachables and container closure integrity testing, in addition to final product monitoring in the established stability program.

Stability

Stability data submitted to STN BL 125487/0 supported a final container shelf-life of 24 months when stored at 2 – 8°C. During this 24 month shelf-life, the product may be stored for up to 6 months at room temperature, not to exceed 30°C. The available stability data indicated no negative trends during the observed long-term storage period. The reconstituted product may be stored at b(4)–30°C for up to 3 hours.The product should be protected from light. Drug substance stability data supported its storage for up to ------b(4)----------

Adventitious Agents Safety

Non-viral pathogen safety

Microbial safety is ensured through control of –b(4)------- in source materials, adherence to current Good Manufacturing Practice, in-process quality control monitoring, validated sterile filtration and aseptic filling processes, and release and stability testing for sterility and endotoxin.

Viral safety

All –b(4)----- have been demonstrated to be free of infectious viruses. The manufacturing process does not use animal-derived raw materials. The –b(4)---------- production campaign is directly tested for infectious virus on relevant –b(4)----- systems. The manufacturing process incorporates a detergent inactivation step, a 15 nm nanofiltration step and a column chromatography step, which collectively have been validated to –b(4)----------. The viral safety profile for ELOCTATE™ is considered acceptable.

b) CBER Lot Release and In-support testing

Routine lot-by-lot release by CBER is not required for ELOCTATE™ because it is a recombinant product.

The Division of Biological Standards and Quality Control has performed in-support testing of commercial scale ELOCTATE™ product lots of 250 IU, 750 IU, 1000 IU and 3000 IU nominal potencies. Test results were deemed consistent with the proposed commercial release specification.

c) Facilities review and inspection

The manufacture of BDD-rFVIIIFc drug substance is performed at Biogen Idec's Cambridge, Massachusetts facility. Manufacture of the drug product is performed at the contract manufacturer, --b(4)----------. Manufacture of the diluent is performed at the contract manufacturer, --b(4)----------

Biogen Idec Cambridge, Massachusetts facility (FEI # 1220951)

The Cambridge site includes –b(4)- buildings used in the manufacture of BDD-rFVIIIFc drug substance: ---b(4)---------- is the primary location for BDD-rFVIIIFc drug substance manufacture. –b(4)----------. This facility is currently used to manufacture three other licensed commercial drug products –b(4)----------. This facility was inspected by CDER/FDA from October 14 to 18, 2013 and by ORA/FDA from July 26 to September 8, 2010 and March 4 to 15, 2013. The three inspections were all classified as, "Voluntary Action Indicated (VAI)."

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CBER Pre-license Inspection

The inspections of Biogen Idec's facility in Cambridge, Massachusetts, and –b(4)- facilities in -b(4)----------, were waived per SOPP 8410.

d) Environmental Assessment

The BLA included a request for a categorical exclusion from an Environmental Assessment under 21 CFR § 25.31(c). The FDA concluded that this request was justified as the manufacture of this product will not alter, significantly, the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Recommendation

The manufacturing process for ELOCTATE™ is considered validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of commercial product meeting acceptable release specification. The reviewers from the Division of Hematology in the Office of Blood Research and Review, and reviewers from the Division of Manufacturing and Product Quality and the Division of Biological Standards and Quality Control in the Office of Compliance and Biologics Quality have concluded that Biogen has provided sufficient data and information on chemistry, manufacturing and controls to support licensure of ELOCTATE™.

4. Nonclinical Pharmacology/Toxicology

a) Pharmacological/Toxicological Findings

The safety and pharmacologic activity of B-domain deleted, recombinant Factor VIII, Fc fusion protein (BDD-rFVIIIFc), the active ingredient in ELOCTATE™, for its intended clinical uses was supported by a series of *in vitro*, *in vivo*, and *ex vivo* studies in genetically modified, Factor VIII-deficient hemophilic mice and dogs (i.e., HemA mice or HemA dogs), and Factor VIII-replete (wild-type) –b(4)-------- monkeys and rats. Procoagulant activity of BDD-rFVIIIFc and two other, recombinant antihemophilic factor concentrate comparators was assessed at clinically relevant and supra-physiologic doses in HemA mice and HemA dogs, using doses 0.5 to 10-fold greater than the recommended clinical dose of 100 IU/kg. Hemophilic animals dosed with BDD-rFVIIIFc showed dose-related decreases in clotting times, which persisted for longer durations than those in HemA mice or dogs dosed with the comparators. Furthermore, *ex vivo* clotting activity in blood samples obtained from HemA mice dosed with BDD-rFVIIIFc was maintained approximately 2-fold longer than clotting activity in blood from HemA mice dosed with either of

the two comparators. Finally, dosing HemA mice with BDD-rFVIIIFc in a regimen simulating human prophylactic dosing decreased both blood loss and the incidence of re-bleeding, and increased survival compared to HemA mice dosed prophylactically with a comparator antihemophilic factor concentrate. The results from these pharmacodynamic studies established the expected biological activity of BDD-rFVIIIFc, and support the proposed indications for: (1) control and prevention of bleeding episodes, (2) perioperative management (surgical prophylaxis) and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes, in patients with Hemophilia A.

Because ELOCTATE™ contains a controlled level of a non-processed, single chain, BDD-rFVIIIFc, the potential of the non-processed protein to impact the function and effectiveness of the final product was evaluated in HemA mice. Clotting times in HemA mice dosed with BDD-rFVIIIFc containing varying amounts of the non-processed, single chain molecule were not affected by its presence at levels of up to 20 to 30% in the ELOCTATE™ drug product. Dosing of HemA mice with non-processed BDD-rFVIIIFc alone also resulted in effective blood clotting; however, re-bleeding occurred more frequently in these animals than in HemA mice dosed with the ELOCTATE™ drug product.

Safety pharmacology evaluations were conducted as part of two repeat-dose toxicity studies of BDD-rFVIIIFc in –b(4)----- monkeys following dosing with –b(4)-- or lyophilized BDD-rFVIIIFc. There were no significant changes or perturbations in cardiac or respiratory function when compared to monkeys dosed with the vehicle control article.

Pharmacokinetic (PK) studies were conducted with clinically relevant doses of ---b)(4)--- and lyophilized BDD-rFVIIIFc or the rFVIII comparators in HemA dogs, in wild-type rats and in -b(4)---------- monkeys. Overall, the elimination half-life ($t_{½}$) for BDD-rFVIIIFc was approximately 2-fold greater than for the comparator, unmodified rFVIII proteins. Specifically, the $t_{½}$ for BDD-rFVIIIFc in HemA dogs was 15.4 hr. compared to 7.4 hr. for the unmodified rFVIII comparator. Toxicokinetics were evaluated in the repeat-dose toxicology studies using lyophilized or -b(4)- BDD-rFVIIIFc. Factor VIII exposures, as determined by estimating the area under the concentration-time curve (AUC), were similar for both formulations. These results also confirmed that clinically relevant or larger exposures to BDD-rFVIIIFc were achieved for the 28 day duration of the repeat-dose toxicology studies in –b(4)------- monkeys, and for up to approximately 14 days in rats. The $t_{½}$ values for BDD-rFVIIIFc in –b(4)------ monkeys were similar regardless of whether the animals were dosed with the -b(4)- or lyophilized BDD-rFVIIIFc formulations, and were slightly longer than the $t_{½}$ values obtained for the comparator rFVIII products. Taken together, these data corroborated that the lyophilized formulation of ELOCTATE™ provides comparable exposure, safety and effectiveness (i.e., procoagulant activity) to the-b(4)- BDD-rFVIIIFc formulation used in the early animal testing and clinical trials, and that no adjustments are required for clinical dosing with the lyophilized product.

Results from PK studies conducted in transgenic mice expressing the human FcRn receptor and in knock-out mice deficient for the FcRn receptor suggested that the extended $t_{½}$ of ELOCTATE™ is mediated via binding of the Fc moiety of BDD-rFVIIIFc to the FcRn receptor. The presence of FcRn was shown to increase the $t_{½}$ of BDD-rFVIIIFc; specifically, the $t_{½}$ of BDD-rFVIIIFc in transgenic mice expressing human FcRn was 10.65 hr., compared to a $t_{½}$ of 4.3 hr. for unmodified rFVIII, which does not contain the Fc moiety. PK results from FcRn

knock-out mice, which do not express the FcRn receptor, revealed no difference in the $t_{½}$ values after dosing with BDD-rFVIIIFc or unmodified rFVIII. Taken together, these data suggest that the increased $t_{½}$ for BDD-rFVIIIFc (compared to the $t_{½}$ values for the unmodified coagulation factors without the Fc moiety) can be attributable to binding and retention of the Fc moiety by the FcRn receptor.

There were no remarkable toxicities reported in –b(4)------ monkeys following a single, intravenous dose of 20,000 IU/kg of BDD-rFVIIIFc, or approximately 200 times the recommended clinical dose, when scaled on a body weight basis. No treatment-related local or systemic toxicities were observed following repeat dosing of rats or –b(4)------ monkeys with BDD-rFVIIIFc for 28 days, at doses ranging from 50 to 1000 IU/kg/dose (approximately 0.5- to 10-fold greater than the intended clinical dose of 100 IU/kg). Results from repeat-dose toxicology studies identified minimal and acceptable findings following administration of lyophilized BDD-rFVIIIFc in –b(4)------- monkeys or -b(4)-- BDD-rFVIIIFc in rats, including non-dose related variations in red blood cell and neutrophil counts, decreases in total protein and albumin, and increases in globulin levels. The increased globulin levels in both rats and -b(4)---------- monkeys correlated with development of antibodies directed against BDD-rFVIIIFc; in the rat study, development of anti-BDD-rFVIIIFc antibodies led to loss of exposure in the majority of animals by day 14. Pronounced subcutaneous bleeding and moribund condition following dosing with 1000 IU/kg of the -b(4)-- BDD-rFVIIIFc formulation led to premature termination of three of ten monkeys in this 28 day repeat-dose study. These adverse findings were not directly related to toxicity of BDD-rFVIIIFc, but were secondary to the formation of anti-BDD-rFVIIIFc antibodies that neutralized endogenous FVIII. In a subsequent study, monkeys dosed daily with the lyophilized BDD-rFVIIIFc (clinical formulation of ELOCTATE™) also developed low titers of anti-BDD-rFVIIIFc antibodies, but maintained high exposure levels for the entire 28 day duration of the study and did not exhibit any toxicities at the highest dose of 1000 IU/kg. These data, together with the PK results from the phase 1 clinical trial were used to calculate margins of safety for BDD-rFVIIIFc of greater than 11 and greater than 26 for the proposed clinical uses, based on AUC and peak concentration (C_{max}) values, respectively.

Specific local tolerance studies in rabbits to evaluate edema and inflammation at the BDD-rFVIIIFc injection sites were not conducted. Instead, an assessment of the injection sites was performed in –b(4)----- monkeys both during and after each 28 day repeat-dose toxicity study testing -b(4)-- or lyophilized BDD-rFVIIIFc formulations. There was no effect on local tolerability at the BDD-rFVIIIFc injection sites regardless of formulation, when compared to the vehicle control group.

Extractables and leachables studies were performed with the matrix used to affinity purify BDD-rFVIIIFc, and showed that the major extractable component was the affinity ligand. The safety of the affinity ligand was appropriately qualified by genotoxicity (-b(4)-) testing and a single dose intravenous toxicity study in rats, with no adverse findings in either study.

The results from the acute and repeat-dose toxicology studies in –b(4)---------- monkeys yielded no observable adverse effect levels (NOAELs) of 20,000 IU/kg for a single, intravenous dose of -b(4)-- BDD-rFVIIIFc, and 1000 IU/kg/day for 28 days of dosing with lyophilized BDD-rFVIIIFc, respectively. These NOAEL claims are based on sound scientific data, and provide an

approximate margin of safety for the lyophilized BDD-rFVIIIFc of 10-fold over the intended clinical dosing regimen of 100 IU/kg for prophylactic use, and of approximately 200-fold (based on the single dose NOAEL of 20,000 IU/kg in –b(4)------- monkeys) over the same clinical dose for emergent use. This margin of safety, in addition to margins of safety calculated based on AUC and C_{max}, suggests that ELOCTATE™ can be administered prophylactically or on-demand in the Hemophilia A population with minimal risk to patient safety.

b) Recommendation

The pharmacology, pharmacokinetic, and toxicology results from the nonclinical development program suggest that treatment of Hemophilia A patients with ELOCTATE™ will be reasonably safe for use for the labeled clinical indications, and support the approval of STN BL 125487/0.

5. Clinical Pharmacology

a) Mechanism of Action

ELOCTATE™ is a recombinant fusion protein that temporarily replaces the missing Coagulation Factor VIII needed for effective hemostasis. ELOCTATE™ contains the Fc region of human immunoglobulin G_1 (IgG_1) that binds to neonatal Fc receptor (FcRn). This receptor is part of a naturally occurring pathway that protects immunoglobulins from lysosomal degradation by cycling them back into circulation, and prolonging their plasma half-life.

b) Pharmacokinetics

Three pharmacokinetic (PK) studies of ELOCTATE™ were conducted in previously treated patients (>12 years old) with severe Hemophilia A. ELOCTATE™ was administered as an intravenous (IV) infusion over approximately 10 minutes. PK profiles were determined by both one stage clotting and chromogenic substrate assays. In the Phase 1/2a study, two single doses were administered intravenously, either 25 IU/kg to six subjects or 65 IU/kg to nine subjects. The mean clearance values (mL/kg/h) were estimated as 1.72 for subjects receiving 25 IU/kg and 2.55 for subjects receiving 65 IU/kg. In the Phase 3, pivotal study, a PK subgroup of 28 subjects received a single dose of 50 IU/kg. The mean, incremental, *in vivo* recovery (IVR) was calculated as 2.26 IU/dL per IU/kg. Mean clearance was estimated to be 2.06 mL/h/kg. The terminal half-life of 19.7 hr. was consistent with results of the Phase 1/2a study. During repeated dosing, ELOCTATE™ PK profiles were comparable at week 14 with the PK profile obtained after the first dose. The PK profiles and estimated parameters for adolescents (12 to <18 years of age) were similar to adults. The ongoing pediatric study has assessed PK profiles in 27 pediatric, previously treated patients (2 to <12 years of age) at a dose of 50 IU/kg. Although, no clinically relevant differences between adults and children 6 to 12 years of age were observed, there was a 58% relative increase in mean body weight adjusted CL. This difference should be taken into account when dosing children 2 to <6 years of age. PK parameters were comparable whether derived from one stage clotting or chromogenic substrate assays.

c) Recommendation

Clinical Pharmacology data were adequate to support licensure of ELOCTATE™.

6. Clinical Safety and Efficacy

a) Clinical Program

Summary of Clinical Studies

The clinical development program to support licensure of ELOCTATE™ is summarized in Table 3.

Table 3: Summary of Clinical Studies

Trial ID (Type of Study)	Study Design	Objective	Subjects	Regimen	Treatment duration
998HA101 (Safety, PK)	Open-label, multicenter, dose escalation; active comparator	To evaluate safety and tolerability of a single administration of two doses of ELOCTATE™	PTPs ≥12 years with severe Hemophilia A 19 enrolled; 16 completed	PK Single dose: 25 or 65 IU/kg IV	1 day; 28-day follow-up
997HA301 (Safety, Efficacy, PK)	Open-label, multicenter, partially randomized, uncontrolled; active comparator for sequential PK subgroup	To evaluate efficacy of ELOCTATE™ for individualized prophylaxis, weekly prophylaxis, episodic (on-demand) dosing, and perioperative management	PTPs ≥12 years with severe Hemophilia A 165 enrolled; 153 completed	Arm 1 (individualized prophylaxis) Initial: twice weekly dosing with 25 IU/kg on Day 1 and 50 IU/kg on Day 4. Thereafter: 25 to 65 IU/kg every 3 to 5 days. **Sequential PK subgroup:** single dose of 50 IU/kg Arm 2 (fixed weekly prophylaxis) 65 IU/kg every 7 days Arm 3 (on-demand) Initial dose of 10 to 50 IU/kg, per treatment guidelines Surgery Based on individual PK	75 weeks for subjects in the sequential PK subgroup; 67 weeks for all other subjects for screening, treatment, and follow-up
8HA02PED (Safety, Efficacy, PK)	Open-label, multicenter, nonrandomized, uncontrolled	To evaluate safety, efficacy and PK in pediatric patients	PTPs <12 years with severe Hemophilia A 50 planned (25 subjects <6 years of age; 25 subjects	Routine prophylaxis Initial dose: 25 IU/kg on Day 1 and 50 IU/kg on Day 4; thereafter dosing can be adjusted to 20 to 40 IU/kg for	30 weeks for treatment and follow-up periods (at least 50 EDs)

Trial ID (Type of Study)	Study Design	Objective	Subjects	Regimen	Treatment duration
			6 to <12 years of age); 33 enrolled as of 04 Jan 2013; 0 completed	Day 1 and 40 to 60 IU/kg for Day 4, up to a maximum of 80 IU/kg every 3 days	
8HA01EXT	Open-label, multicenter, long-term extension study, uncontrolled	To evaluate the long-term safety and efficacy of ELOCTATE™	Adult and pediatric PTPs with severe Hemophilia A 194 planned; 150 enrolled as of 07 Jan 2013; 0 completed	<u>Routine prophylaxis</u> Individualized: 25 to 65 IU/kg every 3 to 5 days, or 2 times per week at 20 to 65 IU/kg Weekly: 65 IU/kg once weekly <u>Surgery</u> Based on individual PK	Up to 4 years or until commercially available in participating countries

Abbreviations: ED = exposure days; IU/kg = international units per kilogram; IV = intravenous; PK = pharmacokinetic; PTP = previously treated patients

In the pivotal trial 997HA301, a total of 164 adolescents and adult subjects from the age of 12 years were enrolled and treated with at least one dose of ELOCTATE™, including 13 adolescents, 12 to <18 years of age (eight subjects were ≥12 to <16 years). The primary objectives of this trial were to evaluate: (1) the safety and tolerability of prophylaxis, on-demand, and surgical treatment regimens, (2) the efficacy of the tailored prophylaxis regimen, and (3) the efficacy of on-demand and surgical treatment regimens. Subjects who entered the study on prophylaxis were allocated to Arm 1 (individualized prophylaxis). Subjects entering the study using ELOCTATE™ episodically or "on-demand" were allowed to choose to enter Arm 1 or to be randomized to Arm 2 (fixed weekly prophylaxis) or Arm 3 (episodic dosing). Analyses for efficacy and safety were done on the full analysis dataset, which included all subjects who were treated with ELOCTATE™.

All subjects were males with severe Hemophilia A (FVIII≤1%) and >150 previous exposure days (EDs) to FVIII therapies. The median age was 30 years (range 12 to 65 years). A total of 87 subjects (53%) were previously treated with prophylaxis regimens of FVIII. Approximately 75% of these subjects were treated with recombinant FVIII, and 87% received prophylaxis regimens of three times per week. The majority of the subjects were White (65%); the second-largest group was Asian (26%). The highest enrolling countries were the United States (54 subjects), United Kingdom (20 subjects), South Africa (17 subjects), India (15 subjects), and Japan (14 subjects).

Twelve subjects were discontinued from the trial, including five subjects who were discontinued as a result of adverse events (AEs):

- Subject 905-002 (Arm 1): due to fatal drug overdose

- Subject 140-003 (Arm 2): due to AE of recurrent arthralgia, but was recorded as having discontinued due to withdrawal of consent. The investigator classified the relationship for both events of mild arthralgia as drug related.
- Subject 360-001 (Arm 2): due to an AE of mild rash on Study Day 1. The investigator classified the relationship as drug related.
- Subject 904-002 (Arm 2): due to an AE of severe femur fracture.
- Subject 422-004 (Arm 2): due to withdrawal of consent in the context of multiple AEs. During the trial, this subject reported lower abdominal pain, malaise, chest pain, cough, angiopathy, arthralgia, hypertension, and myalgia, which were all assessed as mild, not serious, and related to treatment. Following his withdrawal, the subject was noted to have BP elevations and longitudinal follow-up was planned.

The reasons for discontinuation by the remaining seven subjects were: poor compliance (two subjects), voluntary withdrawal of consent (three subjects), incarceration (one subject) and international travel (one subject).

Interim results from ongoing pediatric and extension studies were included in the assessment of safety.

b) Efficacy Analysis

The clinical efficacy of ELOCTATE™ for reducing the number of acute bleeding events per year on prophylactic treatment when compared to on-demand treatment, for the treatment of breakthrough bleeds and perioperative management was assessed in 163 evaluable subjects using the following endpoints:

a) Annualized bleeding rate (ABR; bleeding episodes per patient per year) of prophylaxis (individualized and fixed weekly) vs. on-demand treatment
b) Hemostatic effect for perioperative management using the following, pre-specified, four-point rating scale:
    1. Excellent: Intraoperative and postoperative blood loss similar to (or less than) the non-hemophilic patient
        - No extra doses of ELOCTATE™ needed, and
        - Blood component transfusions required are similar to non-hemophilic patient
    2. Good: Intraoperative and/or postoperative bleeding slightly increased over expectations for the non-hemophilic patient, but the difference was not clinically significant
        - Intraoperative blood loss no more than 250 mL greater than expected for a non-hemophilic patient, and
        - No extra doses of ELOCTATE™ needed, and
        - Blood component transfusions required are similar to non-hemophilic patient
    3. Fair: Intraoperative and/or postoperative blood loss is increased over expectation for the non-hemophilic patient and additional treatment was needed
        - Intraoperative blood loss 250 to 500 mL greater than expected for person without hemophilia, or
        - Extra dose of ELOCTATE™ needed, or

- Increased blood component transfusion required

4. Poor/none: Significant intraoperative and/or postoperative bleeding that was substantially increased over expectations for the non-hemophilic patient, required intervention, and was not explained by a surgical/medical issue other than hemophilia
   - Intraoperative blood loss >500 mL greater than for the non-hemophilic patient, or
   - Unexpected hypotension or transfer to intensive care unit due to bleeding, or
   - Substantially increased blood component transfusion requirement

c) The number of injections and dose per injection required for treatment of acute bleeding

One subject in Arm 2 did not contribute data for the efficacy period because the subject withdrew after the PK evaluation.

Control and Prevention of Bleeding

Control and prevention of bleeding was assessed in subjects enrolled in Arms 1, 2 and 3. A total of 757 acute bleeds were reported in 106 (65%) subjects. The median dose for treatment of a bleed was 27 IU/kg. Overall, 98% of bleeding episodes were controlled with one or two infusions, including 661 (87%) that were controlled with a single infusion. Four subjects required ≥4 infusions:

- Subject 140-004 (Arm 1) required five infusions to treat a spontaneous joint bleed of his right hand on Study Day 157. Results of inhibitor testing were negative. The only other bleeding event for this subject was controlled by a single injection.
- Subject 587-002 (Arm 1) required six infusions to treat a presumed joint bleed of the hip after he was hospitalized for hip pain on study Day 85. Radiologic imaging showed no definite pathology of the hips, no evidence of bleeding into the hips, fracture, or effusion, but possible inflammation of the left iliopsoas muscle. Results of inhibitor testing were negative. All other bleeding events in this subject required a single injection.
- Subject 401-002 (Arm 3) required seven infusions to treat a spontaneous muscle and tissue bleed in his leg on Study Day 66. Results of inhibitor testing were negative. All other bleeding episodes in this subject during the study were controlled with <4 injections.
- Subject 925-001 (Arm 3) required five infusions to treat a spontaneous left hip joint bleed on Study Day 21. Results of inhibitor testing were negative. All other bleeding episodes in this subject during the study were controlled with <4 injections.

Perioperative Management

Data from nine major surgeries in nine subjects aged 27 to 56 years were assessed. Major surgery was defined as any surgical procedure (elective or emergent) that involved general anesthesia and/or respiratory assistance in which a major body cavity is penetrated and exposed, or for which a substantial impairment of physical or physiological functions is produced (e.g., laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation). The indications for surgery were: laparoscopic inguinal hernia repair (n=2), bilateral knee replacement surgery (n=1), knee replacement (n=3), knee revision (n=1), appendectomy (n=1), and arthroscopy (n=1). The median dose per infusion was 51 IU/kg (range 50 – 77 IU/kg). The median consumption was 80 IU/kg on the first day of surgery, 161 IU/kg for the subsequent 3 days, and 387 IU/kg for Days 4 through 14 following surgery. Hemostasis was rated as excellent (n=8) or

good (n=1) for all surgeries. Transfusion support of two units of red blood cells was required for one 26 year-old subject who underwent a bilateral knee replacement. The estimated blood loss was 500 mL intraoperatively and an additional 1100 mL from both surgical drains postoperatively. The subject received one unit each on Days 3 and 4 postoperatively. The hemostatic response was rated as excellent by the Investigator.

In addition, data from 14 minor surgeries that were performed in 12 subjects aged 16 to 62 years were provided as supportive evidence. The indications for the 12 minor surgeries evaluated for efficacy were: dental procedures (n=8), cystoscopy (n=3), and gastroscopy/colonoscopy (n=1). Hemostasis was rated as excellent (n=11) or good (n=1) for all minor surgeries.

Routine Prophylaxis

The hemostatic efficacy of individualized prophylaxis with ELOCTATE™ (Arm 1) was evaluated against on-demand therapy (Arm 3). For subjects on individualized prophylaxis, treatment with ELOCTATE™ resulted in a 95% reduction in the median ABR compared to on-demand therapy (Table 4). The final median weekly dose achieved for subjects on study for at least 6 months was 51 IU/kg (range: 25 to 69 IU/kg). The median interval, when averaged over all dosing intervals, was 3.5 days (range: 2.9 to 5 days). Among the 112 subjects treated for at least 6 months, 111 (99%) achieved a dosing interval of three days or longer, 39 (35%) achieved a dosing interval of four days or longer, and 33 (29%) achieved a dosing interval of five days or longer during the last three months on study. No bleeding episodes were reported for 53 (45%) subjects in Arm 1.

The hemostatic efficacy of fixed weekly prophylaxis with ELOCTATE™ (Arm 2) was also evaluated against on-demand therapy (Arm 3). For subjects treated with weekly prophylaxis, treatment with ELOCTATE™ resulted in an 89% reduction in their median ABR (Table 4). Among the 23 subjects treated with a fixed weekly dosing regimen, no bleeding episodes were reported for four (17%) subjects. Four subjects had an ABR greater than 20. All testing for inhibitors was negative in these patients.

Using a negative binomial model to analyze the annualized bleeding rate (ABR), there was a statistically significant reduction in ABR of 92% ($p<0.001$) for subjects in the individualized prophylaxis arm and a statistically significant reduction of 76% ($p<0.001$) for subjects in the weekly prophylaxis arm compared to the episodic (on-demand) arm.

Table 4: Median ABRs by Treatment Regimen, Site and Cause of Bleed

Etiology	Median ABR			Differences in ABR (%)	
	Individualized Prophylaxis (n=117)	Weekly Prophylaxis (n=23)	On-demand (n=23)	Individualized vs. on-demand	Weekly vs. on-demand
Overall	1.60	3.59	33.57	95	89
Joint	0	1.93	22.76	100	91
Spontaneous	0	1.93	20.24	100	90
Traumatic	0	1.69	9.25	100	82

c) Safety Analysis

The safety of ELOCTATE™ was assessed using the following endpoints: frequency of adverse events, vital signs, clinical laboratory tests, history and physical examinations and immunogenicity

testing. Adverse events (AEs) were coded using MedDRA Version 15.0 and were analyzed based on the principle of treatment emergence during study treatment.

Data from the completed pivotal (997HA301) and PK (998HA101) trials, as well as the ongoing pediatric (8HA02PED) and extension (8HA01EXT) trials were reviewed to allow for an integrated analysis of the safety profile of ELOCTATE™. As of February 8, 2013 (120-day safety update), a total of 164 adult and adolescent, and 43 pediatric PTPs had received at least one infusion of ELOCTATE™ as part of either on-demand treatment of bleeding episodes, perioperative management, routine prophylaxis, or PK evaluation.

There was one unrelated death due to suicide from drug overdose in a 20 year old subject with a history of depression, drug addiction (possibly including heroin), and overdose. Concomitant medications were reported to include methadone, sertraline, alprazolam, and buprenorphine/naloxone. On Study Day 235, the subject was reported to be depressed and had slurred speech. On Day 236, the subject was found dead at his home; resuscitation efforts were unsuccessful. Comprehensive postmortem toxicology studies showed overdose with alprazolam, methadone, morphine, sertraline, and marijuana. The death certificate and autopsy ruled the death a suicide from multiple drug overdose.

Adverse Events

A total of 288 AEs were reported in 108 subjects (66%) during the pivotal trial. As of February 8, 2013, 135 AEs have been reported in 71 subjects (47%) enrolled in the extension trial, and 42 AEs have been reported in 17 (39%) subjects enrolled in the pediatric trial. The most common adverse reactions, (incidence ≥0.6%) from clinical trials were: arthralgia, malaise and abdominal pain at 1.2% each, or chest pain, feeling cold, feeling hot, dizziness, dysgeusia, headache, joint swelling, myalgia, angiopathy, hypertension, bradycardia, hypotension, cough, and rash at 0.6% each. There were 32 SAEs reported during the pivotal, pediatric and extension trials, which were considered unrelated to the product by both the investigator and the FDA reviewer.

Table 5: Serious Adverse Events from Clinical Trials

Trial	Preferred Term	Study Day	Severity	Relationship to ELOCTATE™
997HA301	Nephrolithiasis	149	Moderate	Not related
997HA301	Respiratory distress	32	Severe	Not related
997HA301	Inguinal hernia	184	Mild	Not related
997HA301	Tooth disorder	219	Moderate	Not related
997HA301	Face injury	62	Severe	Not related
997HA301	Restless legs syndrome	221	Severe	Not related
997HA301	Lumbar spinal stenosis	145	Moderate	Not related
997HA301	Syncope	121	Severe	Not related (same subject for these 2 SAEs)
997HA301	Back pain			
997HA301	Hemarthrosis	85	Severe	Not related (same subject for these 3 SAEs)
997HA301	Myalgia	170	Moderate	
997HA301	Femur fracture	51	Severe	Not related
997HA301	Overdose	235	Severe	Not related (same subject for these 2 SAEs)
997HA301	Completed suicide			
997HA301	Tachycardia	161	Severe	Not related (same subject for these 3 SAEs)
997HA301	Hypertensive emergency		Severe	
997HA301	Tachycardia	164	Moderate	
997HA301	Inguinal hernia	71	Mild	Not related
997HA301	Appendicitis	86	Severe	Not related

Trial	Preferred Term	Study Day	Severity	Relationship to ELOCTATE™
8HA01EXT	Hydrocephalus	22	Severe	Not related
8HA01EXT	Head injury	10	Severe	Not related
8HA01EXT	Spinal osteoarthritis	14	Severe	Not related (same subject for these 2 SAEs)
8HA01EXT	Hemorrhagic gastritis	179	Severe	
8HA01EXT	Joint dislocation	222	Severe	Not related
8HA01EXT	Nerve compression	211	Moderate	Not related
8HA01EXT	Influenza	362	Mild	Not related
8HA01EXT	Device dislocation	75	Severe	Not related
8HA01EXT	Depression	196	Severe	Not related
8HA01EXT	Traumatic hematoma	110	Moderate	Not related
8HA01EXT	Post-procedural hemorrhage	76	Moderate	Not related
8HA02PED	Port-a-cath Infection	1	Moderate	Not related (same subject for these 2 SAEs)
8HA02PED	Port-a-cath Infection			

d) Immunogenicity

In all trials, subjects were monitored for neutralizing antibodies to FVIII by the –b(4)----- modification of the Bethesda inhibitor assay, and binding antibodies to BDD-rFVIIIFc by validated –b(4)---------- assay. A subject was considered to have developed an inhibitor if the titer was ≥0.6 Bethesda Units (BU)/mL.

Overall, 11 (6.7%) subjects were found to have positive, non-neutralizing anti-drug antibodies (ADA) during the pivotal trial. Five subjects were positive at baseline and in all cases ADA titers declined during the course of the study; the antibody was no longer detected in two of five subjects at the final visit. Six subjects changed ADA status from negative to positive; the positive result was followed by a negative result in four subjects, and was detected at the last study visit for two subjects. All positive samples were reactive to BDD-rFVIIIFc and full-length rFVIII but not to Fc (IgG_1).

No subject in any of the clinical trials developed confirmed, neutralizing antibodies to Factor VIII. In the pivotal trial (997HA301, n=164), one 25 year old subject developed a transient, positive, neutralizing antibody of 0.73 BU at week 14, which was not confirmed upon repeat testing 18 days later and thereafter. This subject also developed transient anti-BDD-rFVIIIFc binding antibodies at the same time point. No clinical adverse findings were observed and FVIII activity was within the expected range.

e) Pediatric Studies and PREA requirements

ELOCTATE™ received orphan drug designation for the treatment of Hemophilia A on November 23, 2010; therefore, STN BL 125487/0 is exempt from PREA.

The safety and efficacy of ELOCTATE™ in children is being evaluated in an ongoing safety, efficacy, and PK pediatric study of PTPs <12 years of age. A total of 43 subjects have received at least one dose of study drug, including 17 subjects <6 years of age and 35 subjects, 6 to <12 years of age. Evaluable PK profiles are available for 27 subjects given a dose of 50 IU/kg of ELOCTATE™, and demonstrated that clearance (based on per kg body weight) was higher in pediatric patients, 2 to <6 years of age. As a result, higher doses per kilogram body weight or more frequent dosing may be needed in these pediatric patients. Efficacy can be extrapolated from pharmacokinetic data to subjects < 2 years of age.

f) Bioresearch Monitoring

Bioresearch monitoring inspections of four clinical investigators participating in pivotal trial 997HA301 did not reveal significant problems that impacted clinical data submitted to STN BL 125487/0.

g) Conclusion

The outcomes of clinical studies support the safety and efficacy of ELOCTATE™ in patients with Hemophilia A for control and prevention of bleeding, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

7. Pharmacovigilance

a) Reports of Serious Adverse Drug Reactions

ELOCTATE™ is not presently marketed in other countries. Consequently, the only adverse events available for analysis are those reported in the clinical studies noted above. Nineteen serious adverse events and one death were reported in the pivotal clinical study (997HA301). In addition, one serious adverse event was reported in the pediatric trial (8HA02PED) and 11 serious adverse events were reported in the extension trial (8HA02EXT). All reported serious adverse events were unlikely related to ELOCTATE™ based on a detailed review of each subject's case report. The single report of death is of a study subject with depression and substance abuse, and autopsy ruled the death a suicide from drug overdose. No study subject met the pre-specified definition of testing positive for a neutralizing FVIII inhibitor.

b) Summary of the Pharmacovigilance Plan

The proposed pharmacovigilance plan includes routine pharmacovigilance described as cumulative analyses in Periodic Safety Update Reports as well as the continuation of two studies – the pediatric trial 8HA02PED and extension trial 8HA01EXT. A future post-marketing study in previously untreated patients (PUPs) is also planned. All three studies are considered clinical post-marketing commitment studies (PMCs), requiring submission to FDA of the study protocol and planned milestones as well as interim and final study reports at pre-specified times. The proposed pharmacovigilance plan also includes enhanced pharmacovigilance activities described as: (a) expedited reporting to regulators of inhibitor development, (b) targeted follow up by questionnaire of the adverse event of interest in spontaneous reports, or (c) other programs where data are being handled or solicited and all clinical trial serious adverse events. The pharmacovigilance plan proposed by Biogen is acceptable.

8. Advisory Committee Meeting

The Division of Hematology in the Office of Blood Research and Review reviewed the information in BL STN 125487/0 and determined that referral to the Blood Products Advisory Committee (BPAC) prior to approval was not needed because: (1) the product's mechanisms of action are well understood and (2) review of the data did not reveal safety or efficacy concerns, or pose unanswered scientific questions that would benefit from advisory committee discussion and recommendation. [FDAAA (HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE)]

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of STN BL 125487/0.

10. Labeling

The proposed proprietary name, ELOCTATE™, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective and determined to be acceptable. The package insert, carton and container labels submitted to BL STN 125487/0 were considered acceptable.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The CBER review committee recommends approval of this BLA. The manufacturing process for ELOCTATE™ is validated and adequately controlled. Efficacy and safety clinical data for ELOCTATE™ supported a favorable benefit/risk determination for the proposed indications:

- Control and prevention of bleeding episodes,
- Perioperative management,
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

b) Benefit/Risk Assessment

Hemophilia A is a blood clotting disorder resulting from one or more mutations in the Factor VIII gene that lead to a deficiency of Factor VIII. Hemophilia A patients are at risk for acute bleeding episodes predominantly into joints, muscles, mucosa, and body cavities. Repeated bleeding into a joint can lead to disabling joint disease. ELOCTATE™ replaces the missing clotting Factor VIII that is needed to achieve hemostasis in bleeding patients with Hemophilia A. In recent years, treatment regimens have shifted from on-demand treatment of bleeding episodes to routine prophylaxis because of observed improvement in long-term, clinical outcomes (such as joint damage). Patients on routine prophylaxis regimens have been non-compliant, however, because of the short half-life of infused Factor VIII (mean 12 hours), necessitating frequent infusions. ELOCTATE™ is designed to provide a Factor VIII to enable less frequent dosing in routine prophylaxis regimens for Hemophilia A patients.

Benefits

The efficacy of ELOCTATE™ has been established for control and prevention of bleeding episodes, perioperative management and routine prophylaxis to prevent or reduce the frequency of bleeding episodes, in clinical studies that enrolled 164 subjects. The terminal half-life of ELOCTATE™ is 19.7 hours compared to 12 hours for licensed antihemophilic factor concentrates. This allows dosing every 4 days instead of 2-3 times weekly, to maintain a plasma level of Factor VIII between 1-3%, a level that has been shown to prevent or reduce the frequency of bleeding. A dosing schedule of every 4 days is considered a major contribution to the improvement of patient care.

Risks

The formation of Factor VIII inhibitors was not observed during the pivotal and the ongoing pediatric or extension studies. Neutralizing antibodies have been reported to occur in PTPs treated with Factor VIII concentrates. One 25 year old subject had a transient, positive, neutralizing antibody of 0.73 BU at week 14, which was not confirmed upon repeat testing 18 days later and thereafter. Even though no subjects developed neutralizing antibodies to Factor VIII in the pivotal clinical study, the potential for developing inhibitors is discussed in the Warnings and Precautions section of the Package Insert (PI). In the ongoing pediatric and extension studies, there have been no reports of inhibitors thus far. In the clinical program for ELOCTATE™ that included 164 subjects, there were no reports of inhibitor formation. No serious adverse events were found to be attributable to ELOCTATE™.

The benefit/risk profile of ELOCTATE™ is favorable. Clinical studies demonstrated the efficacy of the drug for its labeled indications. No serious adverse events were attributable to the drug. Confirmed inhibitor formation was not observed in study subjects,

12. Recommendation for Post-marketing Risk Management Activities

a) Pediatric Requirements

There are no pediatric requirements since this product has orphan designation.

b) Post-marketing requirements under FD&C Act section 505(o)

The safety data reviewed do not substantiate a need for a post-marketing requirement (PMR) or REMS.

c) Post-marketing commitments

Biogen Idec commits to the following:

1. To complete data analysis of the trial 8HA02PED, *An Open-Label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein, BIIB031, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A*, with the following milestones:
    - Trial completed: December, 2013
    - Submission of Final Study Report: September, 2014
2. To complete ongoing trial 8HA01EXT, *An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia A*, with the following milestones:
    - Trial completion date: December, 2018
    - Submission of Final Study Report: September, 2019
3. To complete trial 99HA306, *An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc) in the*

Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia A, with the following milestones:

- Trial completion date: December, 2023
- Submission of Final Study Report: September, 2024

13. References

1. Guidance for Industry: Q8(R2) Pharmaceutical Development, 2009
2. Guidance for Industry: Monoclonal Antibodies Used as Reagents in Drug Manufacturing, 2001